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Schnellauflösliche pharmazeutische Dosierungsformen und Verfahren zu ihrer Herstellung

Formes de dosage pharmaceutiques à délitement rapide et procédé pour leur préparation

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01.02.1995 Bulletin 1995/05(73) Proprietor: **McNEIL-PPC, INC.**
Milltown, New Jersey 08861 (US)(72) Inventor: **Gowan, Jr. Walter G.**
Lansdale, PA 19446 (US)(74) Representative:
Mercer, Christopher Paul et al
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)(56) References cited:
EP-A- 0 317 274 EP-A- 0 459 695
EP-A- 0 523 847 US-A- 4 716 041
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Description**FIELD OF THE INVENTION**

5 [0001] The present invention relates to a rapidly disintegrating pharmaceutical dosage form containing coated pharmaceutical particles and to a process for preparing such dosage forms.

BACKGROUND OF THE INVENTION

10 [0002] Rapidly disintegrating or dissolving pharmaceutical dosage forms are available for human patients who have difficulty swallowing conventional tablets or capsules, and for the sublingual and buccal administration of drugs.

[0003] Freeze-dried or lyophilized dosage forms are generally known to rapidly dissolve or disintegrate in the mouth. These forms consist of a porous matrix of a water-soluble or water-dispersible carrier material which is impregnated with a unit dose of the pharmaceutical active. These dosage forms are prepared by first adding the pharmaceutical active to a solution comprising the carrier material and a suitable solvent, typically water. The resulting composition is then subjected to a freeze drying procedure whereby the solvent sublimes under a high vacuum.

15 [0004] While freeze-dried dosage forms dissolve rapidly, they must be manufactured on expensive lyophilization equipment. Further, these dosage forms have generally only been used with water-insoluble actives that are relatively tasteless, because they disintegrate in the mouth, rather than being swallowed as in the case of conventional tablets and capsules.

20 [0005] Water-soluble drugs are generally avoided in freeze-dried dosage forms because of the dissolution of the drug in the mouth, which results in a bitter or otherwise objectionable taste. Further problems can arise when water-soluble drugs are used because of the formation of eutectic mixtures, which lower the freezing point of the formulation, resulting in incomplete freezing or melting during the freeze-drying process. This phenomenon results in product loss.

25 [0006] M. S. Amer in U.S. Patent 4,866,046, issued September 12, 1989, describes an aspirin tablet that rapidly dissolves in the oral, preferably sublingual, cavity within 2-60 seconds. This tablet provides rapid absorption of aspirin from the saliva into the blood stream. The sublingual tablet is prepared by compressing into slugs a mixture of starch (10% moisture), acetylsalicylic acid, flavor and sweetener. The slugs are then ground (14-16 Mesh size) and recompressed into tablets. An amino acid may also be used with the aspirin for its solubilizing and a taste-neutralizing effects.

30 [0007] U.S. Patent No. 5,082,667, issued January 21, 1992, to K. G. Van Scoik discusses a tablet triturate dosage that quickly dissolves in the buccal cavity. The form includes a porous, cementatory network of a water-soluble but ethanol-insoluble carbohydrate, which contains discrete particles of the active ingredient that have been coated with a triglyceride coating. The discrete particles are prepared by suspending the active ingredient in molten triglyceride. The discrete particles are mixed with the carbohydrate and a temporary liquid binder to form a damp mass. The mass is then shaped into a tablet and dried to form the tablet triturate.

35 [0008] The tablet triturate of Van Scoik is limited to active ingredients, such as estazolam, that are not sensitive to the melting temperature of the triglyceride. Further, since the dosage form is formed into a damp mass and subsequently dried, conventional, compression tableting machines cannot be used to manufacture this product.

40 [0009] J. A. McCarty, in U.S. Patent No. 5,112,616, issued May 12, 1992, discusses a fast dissolving buccal tablet containing a buccally absorbable active ingredient, a pharmaceutically acceptable lubricant and a soluble, directly compressible tablet excipient, such as sucrose or lactose. These ingredients are mixed together and compressed into the final tablet form. Since the active ingredient is not coated, patient compliance, especially in children, would be an issue if the pharmaceutical had a bitter or otherwise objectional taste.

45 [0010] A need, therefore, exists for a rapidly disintegrating dosage form containing taste-masked pharmaceutical particles that can be manufactured without the use of water or solvents, and compressed on conventional tableting machines. This dosage form should be suitable for use with both water-soluble and water-insoluble actives which may have an objectional taste.

SUMMARY OF THE INVENTION

50 [0011] The present invention provides a compressed pharmaceutical dosage form containing at least one pharmaceutical particle coated with a taste-masking composition, a water-disintegratable, compressible carbohydrate and a binder. These components are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to cause the carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing the coated pharmaceutical particle to be swallowed.

[0012] In a preferred embodiment, the pharmaceutical is coated with a blend of a first polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate and a second polymer selected from the group consisting of polyvinyl pyrrolidone and hydroxypropyl cellulose, where the weight ratio of the first polymer to the second pol-

ymers is within the range of about 90:10 to about 50:50.

- 5 [0013] In a further preferred embodiment of the present invention, the compressed pharmaceutical dosage form is prepared by coating the pharmaceutical with the aforementioned blend of first and second polymers in a fluidized bed coating operation. The coated pharmaceutical is dry blended with the water-disintegratable, compressible carbohydrate and the binder, and then compressed into a wafer having a hardness within the range of about 1.0 to about 3.0 kp, whereby the carbohydrate disintegrates after oral administration allowing said coated pharmaceutical to be swallowed.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

- 10 [0014] The compressed pharmaceutical dosage forms of the present invention rapidly disintegrates when contacted by water, saliva and aqueous solutions, and are particularly useful in the oral delivery of drugs. As used in the present invention "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with the aforementioned fluids. These dosage forms generally disintegrate in the mouth within about 30 seconds, and preferably within about 20 seconds or less.
- 15 [0015] The dosage forms contain coated particles comprising at least one pharmaceutical coated with a taste-masking coating, a water-disintegratable, compressible carbohydrate, and a binder. These ingredients are dry blended and then compressed into a mass, preferably a wafer, having a hardness sufficient to cause the carbohydrate to disintegrate after oral administration. Upon disintegration, the coated pharmaceutical particles are released from the dosage form with no objectionable taste and swallowed by the user.
- 20 [0016] Conventional tabletting machines can be used to compress the ingredients into the final dosage form. Since the ingredients are dry blended, water-soluble, as well as water-insoluble, coated pharmaceuticals can be used in the dosage form. Further, in view of the use of a taste-masking coating, pharmaceuticals having an objectional taste may also be used in the present invention.
- 25 [0017] The water-disintegratable, compressible carbohydrate used in the present invention includes carbohydrate materials conventionally used in tablets. The carbohydrates facilitate the breakup of the dosage form after oral administration, and are described in Liberman et al., *Pharmaceutical Dosage Forms*, Marrel Dekker, Inc., New York, 2 Ed. Vol. 1, pp. 205-209 (1990). Preferred water-disintegratable, compressible carbohydrates include mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, and mixtures thereof.
- 30 [0018] The binder in the present invention is used to add cohesiveness to the formulation, thereby providing the necessary bonding to form a cohesive mass or compact upon compression. These binders are conventionally used in direct compression tablets and are described in Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990). Preferred binders include cellulose, cellulosic derivatives, polyvinyl pyrrolidone, starch, modified starch, and mixtures thereof, and, in particular, microcrystalline cellulose available from FMC Corp. under the trademark AVICEL® PH 101.
- 35 [0019] The dosage form of the present invention contains a coated particle containing at least one pharmaceutical active coated with a taste-masking coating. The active may be coated with taste-masking coatings known in the art, such as those described in U.S. Patent No. 4,851,226, issued July 25, 1989, to T.W. Julian, et al.; U.S. Patent No. 5,075,114, issued December 24, 1991 to E.J. Roche; and EP-A-0 523 847. As used in the present invention, "coated particle" refers to a solid pharmaceutical in the form of a crystal or particle, an agglomerate of individual particles, or a granulated particle, which has been coated with the taste-masking composition. The dosage form may provide for immediate or sustained release of the pharmaceutical active.
- 40 [0020] Taste-masking compositions suitable for use as coatings are provided in the following Table:

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	Polymer System	Coat Level¹	Polymer Ratio²
5	Cellulose Acetate/PVP	5-60%	90/10 to 60/40
	Cellulose Acetate Butyrate/PVP	5-60%	90/10 to 60/40
	Cellulose Acetate/HPC	5-60%	90/10 to 50/50
10	Cellulose Acetate Butyrate/HPC	5-60%	90/10 to 50/50
	Cellulose Acetate/EUDRAGIT E100	8-60%	All ratios
	Cellulose Acetate Butyrate/EUDRAGIT E 100	8-60%	All ratios
15	Ethyl Cellulose/PVP	8-60%	90/10 to 60/40
	Ethyl Cellulose/HPC	8-60%	90/10 to 50/50
	Ethyl Cellulose/EUDRAGIT E 100	8-60%	All ratios
20	HPC	10-60%	NA
	HEC	10-60%	NA
	EUDRAGIT E 100	10-60%	NA
	HPMC	10-60%	NA
25	HEC/HPMC	10-60%	All ratios
	HPC/HPMC	10-60%	All ratios
	HEC/HPC	10-60%	All ratios
30	2-vinyl pyridine styrene co-polymer	10-60%	NA
	CA/2-vps	8-60%	All ratios
	CAB/2-vps	8-60%	All ratios
	Ethyl Cellulose/2-vps	8-60%	All ratios
35	Cellulose Triacetate/PVP	8-60%	90/10 to 60/40
	Cellulose Triacetate/HPC Cellulose Triacetate/<->	8-60%	90/10 to 50/50
40	EUDRAGIT E 100	8-60%	All ratios
	PVP - polyvinylpyrrolidone		
	HPC - Hydroxypropyl cellulose		
	HEC - Hydroxyethyl cellulose		
	HPMC - Hydroxypropylmethyl cellulose		
45	CA - Cellulose Acetate		
	CAB - Cellulose Acetate Butyrate		
	2-VPS - 2-Vinyl pyridine styrene		
	EUDRAGIT™ E-100 - methylaminoethyl-methacrylate and neutral methacrylic acid esters available from Rohm Pharma GmbH, Germany.		

50 ¹ Percent by weight of the coated particle in a dried state.

2 By weight.

55 [0021] Substantially all of the pharmaceutical or granulated pharmaceutical should be coated with a layer of taste-masking composition having a thickness of about 3 to about 10 µm. The coating should be substantially free of cracks, holes or other imperfections when examined under a scanning electron microscope at 100-500x.

[0022] The pharmaceutical active is preferably coated with a blend of a first polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate and a second polymer selected from the group consisting of

polyvinyl pyrrolidone and hydroxypropyl cellulose. The weight ratio of the first polymer to the second polymer in this blend is within the range of about 90:10 to about 50:50 and preferably about 90:10 to about 70:30.

[0023] The first polymer of the blend is generally water-insoluble, but is soluble in organic solvents. These polymers provide good taste-masking properties since they do not dissolve in the mouth. However, if used alone, they do not provide adequate bioavailability of the pharmaceutical. To provide the requisite bioavailability, the second polymer, which is soluble in both water and organic solvents, is added to the blend that is used to coat the pharmaceutical active. This blend of first and second polymers provides the balance needed for the taste masking.

[0024] Preferred blends of the first and second polymers include cellulose acetate (CA) and polyvinyl pyrrolidone (PVP) having a weight ratio of CA:PVP within the range of about 90:10 to about 60:40, cellulose acetate (CA) and hydroxypropyl cellulose (HPC) having a weight ratio of CA:HPC within the range of about 90:10 to about 50:50, cellulose acetate butyrate (CAB) and hydroxypropyl cellulose (HPC) having a weight ratio of CAB:HPC within the range of about 90:10 to about 50:50, and cellulose acetate butyrate (CAB) and polyvinyl pyrrolidone (PVP) having a weight ratio of CAB:PVP within the range of about 90:10 to about 60:40.

[0025] Cellulose acetate NF powder, e.g., CA 398-10, CA 320-S or CA 435-75S available from FMC Corp., may be used as the first polymer in the blend. CA 398-10 polymer has an acetyl content of about 39.8 weight percent, a hydroxyl content of about 3.4 weight percent, a degree of substitution of 2.7 and a solution viscosity of about 38 poises or 10 seconds, as determined by ASTM Method D 1343 in the solution described as Formula A, ASTM Method D 871. The typical weight average molecular weight, according to the manufacturer, is 177,000 and the typical number average molecular weight is 58,500. CA 320-S polymer has an acetyl content of about 32.0 weight percent, a hydroxyl content of about 9.0 weight percent and a degree of substitution of 2.1. In a solution of 90:10 CH₂Cl₂:methanol, at 4% (w/w) concentration, the viscosity is 50 centipoise. The typical weight average molecular weight is 100,500 and the typical number average molecular weight is 63,500. CA 435-75S has an acetyl content of about 43.6 weight percent and a hydroxyl content of about 0.9 weight percent.

[0026] Cellulose acetate butyrate, e.g., CAB 171-15S, CAB 381-2 and CAB 500-1 available from FMC Corp., may also be used as the first polymer. CAB 171-15S has a butyryl content of 17 weight percent, an acetyl content of 29.5 weight percent, a hydroxyl content of 1.5 weight percent and a viscosity of 24 centipoises in a 4 weight percent solution of methylene chloride:methanol (90:10) one day after solution preparation at 25°C. CAB 381-2 has a butyryl content of 37 weight percent, an acetyl content of 13 weight percent and a hydroxyl content of 1.5 weight percent. CAB 500-1 has a butyryl content of 50 weight percent, an acetyl content of 5 weight percent and a hydroxyl content of 0.5 weight percent.

[0027] Polyvinyl pyrrolidone (Povidone USP), e.g., PLASDONE® K-25, K-25/28 or K-29/32 from ISP Corporation, may be used as the second polymer in the blend. Povidone K-25 has a viscosity of 2.4 centipoises in a 5% solution of water at a pH 7 and 25°C.

[0028] Hydroxypropyl cellulose, e.g., KLUCEL EF, JF and LF, available from Aqualon Co. may also be used as the second polymer. These polymers generally have a molecular weight of about 80,000 to about 370,000.

[0029] The blend of first and second polymers may be coated directly onto the pure pharmaceutical or may be coated onto a granulated particle containing the pharmaceutical. In the case of a granulated particle, such as a rotogravitated particle, the pharmaceutical active will constitute from about 5 to about 90 weight percent of the particle, with the remainder being the binder or filler. Suitable binders for the granulated particles include polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and other pharmaceutically acceptable polymers. Fillers suitable for use in such granulated particles include lactose, confectioner's sugar, mannitol, dextrose, fructose, other pharmaceutically acceptable saccharides and microcrystalline cellulose.

[0030] The coated particles are prepared by spraying an organic solvent solution of the polymeric blend onto the pharmaceutical, or a granulated particle containing the pharmaceutical, in a fluidized bed, such as a Wurster coater or a rotogravitated. A wide variety of organic solvents may be used to prepare the solution of the polymeric blend. For example, a preferred solvent is a mixture of acetone and methanol, but other solvent systems may be employed, including methylene chloride, methylene chloride-methanol, acetone-ethyl acetate, toluene-ethanol and acetone-ethanol. Generally, the proportion of the polymer blend in the solvent solution will be within the range of about 5 to about 20, preferably about 8 to about 15, weight percent, depending on the solvent and other similar considerations.

[0031] When a fluidized bed coating operation is used, air, which may be heated, passes through a bed of the pharmaceutical solids to fluidize them, and the solution of the polymeric blend is sprayed onto the fluidized bed and thereby coats the pharmaceutical. The air passing through the bed dried the coating onto the pharmaceutical, so that a dry coated granule is obtained.

[0032] Conventional fluidized bed coating equipment is used in the present invention to coat the pharmaceutical or the rotogravitated particle containing the pharmaceutical. This equipment includes Wurster fluid-bed coaters, where the solution of the polymer blend is sprayed from the bottom of the chamber, and a rotogravitated, where the solution of the polymer blend is tangentially sprayed. These coating operations are further described in Liberman et al., Pharmaceutical Dosage Forms, Marcel Dekker, Inc., New York, Vol. 3, pp. 138-150 (1990).

[0033] The coated particle, in a dried state, generally contains about 5 to about 60, preferably about 10 to 40, weight percent of the blend of the first and second polymers. The exact proportions of the coating to the pharmaceutical can, however, vary depending upon the level of taste-masking required and whether a sustained or immediate release of the pharmaceutical is desired. Larger proportions of the coating tend to provide a sustained release effect and enhance taste-masking.

[0034] The dosage form of the present invention may be used to orally administer a wide variety of solid pharmaceutical actives. Pharmaceutical actives which can be used in the dosage form include acetaminophen, ibuprofen, flurbiprofen, naproxen, aspirin, pseudoephedrine, phenylpropanolamine, chlorpheniramine maleate, dextromethorphan, diphenhydramine, famotidine, loperamide, ranitidine, cimetidine, astemizole, terfenadine, terfenadine carboxylate, cetirizine, mixtures thereof and pharmaceutically acceptable salts thereof.

[0035] The pharmaceutical(s) present in the dosage form in a therapeutic effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular compound being administered, the bioavailability characteristics of the pharmaceutical, the dose regime, the age and weight of the patient, and other factors must be considered.

[0036] The dosage form may also contain ingredients other than the coated particles, carbohydrate and binder. The additional ingredients include sweeteners, such as aspartame, sucralose and saccharin; and lubricants, such as magnesium stearate, stearic acid, talc, and waxes. The dosage form may also incorporate pharmaceutical acceptable adjuvants. Such adjuvants, include, for example, preservatives, flavors, antioxidants, surfactants, and/or colors.

[0037] The compressed dosage form, on a dry basis, generally comprises from about 0.1 to about 45, preferably about 12 to about 25, percent by weight of the coated pharmaceutical particle; from about 30 to about 90, preferably about 40 to about 65, percent by weight of the water-disintegratable, compressible carbohydrate material; from about 1 to about 30, preferably about 5 to about 20, percent by weight of the binder; from about 0.1 to about 5, preferably about 0.1 to about 0.5, percent by weight of the lubricant; from about 0.05 to about 5, preferably about 0.1 to about 3.0, percent by weight of the sweetener; from about 0.05 to about 5, preferably about 0.2 to about 2.0, percent by weight of the flavor; and from about 0.01 to about 5, preferably about 0.03 to about 0.3, percent by weight of the color.

[0038] The unit weight of the dosage form will vary depending on the dosage of the active ingredient. The unit weight will generally range from about 250 to about 1500, preferably about 250 to about 1000, mg. A typical dosage form may contain:

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Ingredient	Unit Wt. (mg)
Coated Pharmaceutical Particle	0.5 - 600
Compressible Carbohydrate	250 - 750
Binder	20 - 100
Lubricant	4 - 10
Sweetener	1 - 10
Flavor	1 - 10
Color	1 - 10

45 [0039] In a preferred embodiment of the invention, the dosage form has a size, shape, weight and hardness that allows for it to be introduced into the oral cavity and placed on the tongue, so as to rapidly disintegrate. Generally, the dosage form will be a tablet having a coin-shaped disc or wafer configuration. Preferably, the wafer will have a diameter of about 1.48 cm (7/16 inch) to about 1.91 cm (3/4 inch), preferably about 1.59 cm (5/8 inch), and a thickness of about 0.13 cm (0.05 inch) to about 1.27 cm (0.5 inch), preferably about 0.20 cm (0.08 inch) to 0.64 cm (0.25 inch). While a wafer shape is generally preferred, because it provides a larger surface area to be contacted by the tongue and other moist areas of the oral cavity, other shapes may be employed, such as a cube, triangle and cylinder.

[0040] The dosage form is prepared by forming the coated particles of the pharmaceutical using the aforementioned techniques. The particle size of the coated particles, as well as the remaining components, is generally less than 400, preferably less than 150, μm . Larger particle sizes tend to give the wafer a gritty mouth feel, and should therefore be avoided. The components of the dosage form are then dry mixed to form a uniform powder blend. The blend is then compressed into a mass having the desired shape and hardness using conventional compression tableting techniques.

[0041] The external pressure applied by the tablet press during the compression step is controlled so that the hardness of the dosage form is within the range of about 1.0 to about 3.0, preferably about 1.5 to about 2.5, kp (kiloponds)

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This hardness is measured by conventional pharmaceutical hardness testing equipment, such as a Schleuniger Hardness Tester. Hardnesses within this range provide a dosage form which will rapidly disintegrate when placed in the oral cavity. If the hardness exceeds 3.0 kp, the compressed dosage form will not readily disintegrate in the oral cavity, while hardnesses less than 1.0 kp result in a dosage form exhibiting high friability.

- 5 [0042] Specific embodiments of the present invention are illustrated by way of the following examples. This invention is not confined to the specific limitations set forth in these examples, but rather to the scope of the appended claims. Unless otherwise stated, the percentages and ratios given below are by weight.

EXAMPLE

10 [0043] This Example provides a formulation for making a rapidly disintegrating, compressed wafer that contains acetaminophen coated with a blend of cellulose acetate and polyvinyl pyrrolidone. The weights provided hereinafter are based on a wafer unit weight of 400 mg.

15 [0044] A coating solution containing a blend of cellulose acetate (CA 398-10) and polyvinyl pyrrolidone (Povidone 29/32) was prepared at 12 % solids with an acetone/methanol (80:20) solvent. The ratio of cellulose acetate to polyvinyl pyrrolidone was 85:15.

20 [0045] Four kilograms of acetaminophen (nominal particle size of 300 µm) was charged into a Wurster (bottom spray) fluidized bed coating apparatus. The acetaminophen was then placed in a fluidized state by a flow of air at a temperature of 30°C. The coating solution was then sprayed (atomization air pressure = 3 bar) onto the fluidized acetaminophen particles at a rate of 80 grams/min. until a coated acetaminophen particle containing approximately 12 % by weight of the coating was obtained.

25 [0046] The coated acetaminophen particles were combined with following ingredients to produce the wafers:

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Ingredients	Unit Wt. (mg)
CA/PVP Coated Acetaminophen Particles	91.0
Mannitol (Granular), USP	229.15
Microcrystalline Cellulose, NF	60.0
Aspartame, NF	6.0
Prosweet Powder (Sugarless)	1.5
Color	0.9
Citric Acid, USP	3.0
Flavors	5.2
Colloidal Silicon Dioxide	0.25
Stearic Acid, NF	3.0
Wafer Weight	400.0

45 Dry Blending

[0047]

- 50 1. Screen the color through a 60 mesh screen, the CA/PVP coated acetaminophen particles through a 30 mesh screen and the mannitol through a 12 mesh screen.
2. Mix the microcrystalline cellulose, aspartame, flavors, citric acid, Prosweet, colloidal silicon dioxide and stearic acid by shaking in a container for two minutes.
- 55 3. Blend the color and mannitol in a blender.
4. Place the mixture from Step 2 and the CA/PVP coated acetaminophen particles in blender containing the mixture from Step 3 and blend.

Tablet Compression

[0048]

- 5 1. Compress the blend into wafers to the following specifications on a rotary tablet press equipped with the following tooling:

Punches: 1.59 cm (5/8 inch), flat faced, bevel edge
Dies: 1.59 cm (5/8 inch) round
10 Group Weight (10 wafers): Target - 4.0 grams
 (Range: 360 - 440 milligrams)
 Thickness: Target 2.0 mm (Range 1.8 to 2.2 mm)
 Hardness: Target 2 kp (Range 1.5 to 2.5 kp)

15 2. Collect compressed wafers into a properly labelled container.

[0049] A wafer was placed in on the tongue of a human and was found to disintegrate in less than 30 seconds without a bitter aftertaste.

[0050] Various modifications can be made from the above-described embodiments without departing from the scope of the present invention.

Claims

- 1. A compressed pharmaceutical dosage form, comprising:**

at least one coated particle comprising at least one pharmaceutical coated with a taste-masking coating; a water-disintegrable, compressible carbohydrate; and a binder.

said dosage form having a hardness within the range of about 1.0 to about 3.0 kp and sufficient to cause said carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing said particle to be swallowed.

2. The pharmaceutical dosage form of claim 1 wherein the compressible carbohydrate is mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, or a mixture thereof.

the pharmaceutical dosage form of claim 1 or claim 2 wherein said coated particle comprises at least one pharmaceutical coated with a blend of a first polymer which is a cellulose acetate or cellulose acetate butyrate and a second polymer which is polyvinyl pyrrolidone or hydroxypropyl cellulose, wherein the weight ratio of the first polymer to the second polymer is within the range of about 90:10 to about 50:50.

4. A pharmaceutical dosage form of any one of claims 1 to 3 being a compressed wafer comprising:

coated particles comprising at least one pharmaceutical coated with a blend of a first polymer which is a cellulose acetate or cellulose acetate butyrate and a second polymer which is polyvinyl pyrrolidone or hydroxypropyl cellulose, wherein the weight ratio of the first polymer to the second polymer is within the range of about 90:10 to about 50:50.

90:10 to about 50:50; a water-disintegrable, compressible carbohydrate which is mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, or

a mixture thereof; and
a binder which is cellulose, a cellulosic derivative, polyvinyl pyrrolidone, starch, modified starch or a mixture thereof,

- 55 5. The wafer of claim 4 having a diameter of about 1.48 cm (7/16 inch) to about 1.91 cm (3/4 inch), a thickness of
about 0.13 cm (0.05 inch) to about 1.27 cm (0.5 inch), and a hardness of about 1.5 to about 2.5 kp.

6. The wafer of claim 4 or claim 5 comprising:

about 0.5 to about 600 mg of said coated particles;
about 250 to about 750 mg of said carbohydrate; and
about 20 to about 100 mg of said binder,

5 and which optionally additionally comprises:

about 4 to about 10 mg of a lubricant;
about 1 to about 10 mg of a color;
about 1 to about 10 mg of a sweetener; and
10 about 1 to about 10 of a flavor.

7. The pharmaceutical dosage form of any one of claims 3 to 6 wherein the coated particle comprises about 5 to about 60 percent by weight of the blend of first and second polymers.
- 15 8. The pharmaceutical dosage form of any one of claims 1 to 7 wherein the pharmaceutical is acetaminophen, ibuprofen, flurbiprofen, naproxen, aspirin, pseudoephedrine, phenylpropanolamine, chlorpheniramine maleate, dextromethorphan, diphenhydramine, famotidine, loperamide, ranitidine, cimetidine, astemizole, terfenadine, terfenadine carboxylate, certirizine, a pharmaceutically acceptable salt thereof or a mixture thereof, and wherein preferably the pharmaceutical is acetaminophen, ibuprofen, loperamide, famotidine or aspirin.
- 20 9. A process for preparing a compressed pharmaceutical dosage form, comprising the steps of:

forming at least one coated particle comprising at least one pharmaceutical coated with a taste-masking coating;
25 dry mixing said coated particle with a water-disintegratable, compressible carbohydrate and a binder; and compressing the mixture into a mass having a hardness sufficient to cause said carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing said coated particle to be swallowed; wherein said compressed pharmaceutical dosage form has a hardness within the range of about 1.0 to about 3.0 kp.

30 **Patentansprüche**

1. Gepreßte pharmazeutische Dosierungsform, umfassend: wenigstens einen überzogenen Partikel, der wenigstens ein Pharmazeutikum umfaßt, das mit einer geschmacksmaskierenden Beschichtung überzogen ist; ein in Wasser zerfallendes, preßbares Kohlenhydrat; und ein Bindemittel, wobei die Dosierungsform eine Härte im Bereich von etwa 1,0 bis 3,0 kp und ausreichend aufweist, um zu bewirken, daß das Kohlenhydrat innerhalb 30 Sekunden nach oraler Verabreichung zerfällt und dadurch ermöglicht, daß der Partikel geschluckt wird.
- 35 2. Pharmazeutische Dosierungsform nach Anspruch 1, bei der das preßbare Kohlenhydrat Mannitol, Sorbitol, Dextrose, Saccharose, Xylitol, Lactose oder eine Mischung daraus ist.
- 40 3. Pharmazeutische Dosierungsform nach Anspruch 1 oder Anspruch 2, bei der der überzogene Partikel wenigstens ein Pharmazeutikum umfaßt, das mit einer Mischung aus einem ersten Polymer, das ein Zelluloseacetat oder Zelluloseacetatbutyrat ist, und einem zweiten Polymer, das Polyvinylpyrrolidon oder Hydroxypropylzellulose ist, überzogen ist, wobei das Gewichtsverhältnis des ersten Polymers zu dem zweiten Polymer im Bereich von etwa 90:10 bis etwa 50:50 liegt.
- 45 4. Pharmazeutische Dosierungsform nach einem der Ansprüche 1 bis 3, die ein gepreßtes Plättchen ist, umfassend:
überzogene Partikel, die wenigstens ein Pharmazeutikum umfassen, das mit einer Mischung aus einem ersten Polymer, das Zelluloseacetat oder Zelluloseacetatbutyrat ist, und einem zweiten Polymer, das Polyvinylpyrrolidon oder Hydroxypropylzellulose ist, überzogen ist, wobei das Gewichtsverhältnis des ersten Polymers zum zweiten Polymer im Bereich von etwa 90:10 bis etwa 50:50 liegt; ein in Wasser zerfallendes, preßbares Kohlenhydrat, das Mannitol, Sorbitol, Dextrose, Saccharose, Xylitol, Lactose oder eine Mischung daraus ist; und
55 ein Bindemittel, das Zellulose, ein Zellulosederivat, Polyvinylpyrrolidon, Stärke, modifizierte Stärke oder eine Mischung daraus ist, wobei das Plättchen eine Härte im Bereich von 1,0 bis etwa 3,0 kp aufweist, wodurch das Kohlenhydrat nach oraler Verabreichung zerfällt und ermöglicht, daß die überzogenen Partikel geschluckt werden.

den.

5. Plättchen nach Anspruch 4, das einen Durchmesser von etwa 1,48 cm (7/16 Inch) bis etwa 1,91 cm (3/4 Inch), eine Dicke von etwa 0,13 cm (0,05 Inch) bis etwa 1,27 cm (0,5 Inch) und eine Härte von 1,5 bis 2,5 kp aufweist.

6. Plättchen nach Anspruch 4 oder Anspruch 5, umfassend:

etwa 0,5 bis etwa 600 mg der überzogenen Partikel; etwa 250 bis etwa 750 mg des Kolenhydrates; und etwa 10 bis etwa 100 mg des Bindemittels, und das optional zusätzlich umfaßt: etwa 4 bis etwa 10 mg eines Schmiermittels, etwa 1 bis etwa 10 mg eines Farbstoffes, etwa 1 bis etwa 10 mg eines Süßstoffes; und etwa 1 bis etwa 10 mg eines Aromas.

7. Pharmazeutische Dosierungsform nach einem der Ansprüche 3 bis 6, bei der der überzogene Partikel etwa 5 bis etwa 60 Gew.-% der Mischung aus erstem und zweitem Polymer umfaßt.

15. 8. Pharmazeutische Dosierungsform nach einem der Ansprüche 1 bis 7, bei der das Pharmazeutikum Acetaminophen, Ibuprofen, Flurbiprofen, Naproxen, Aspirin, Pseudoephedrin, Phenylpropanolamin, Chlorpheniraminmaleat, Dextromethorphan, Diphenhydramin, Famotidin, Loperamid, Ranitidin, Cimetidin, Astemizol, Terfenadinecarboxylat, Certirizin, ein pharmazeutisch annehmbares Salz davon oder eine Mischung daraus ist, und bei der das Pharmazeutikum vorzugsweise Acetaminophen, Ibuprofen, Loperamid, Famotidin oder Aspirin ist.

20. 9. Verfahren zur Herstellung einer gepreßten pharmazeutischen Dosierungsform, das die Schritte umfaßt von:

25. Bilden wenigstens eines überzogenen Partikels, der wenigstens ein Pharmazeutikum umfaßt, das mit einer geschmacksmaskierenden Beschichtung überzogen ist; trockenes Mischen des überzogenen Partikels mit einem in Wasser zerfallenden, preßbaren Kohlenhydrat und einem Bindemittel; und Pressen der Mischung in eine Masse, die eine ausreichende Härte aufweist, um zu bewirken, daß das Kohlenhydrat innerhalb 30 Sekunden nach oraler Verabreichung zerfällt und dadurch ermöglicht, daß die überzogenen Partikel geschluckt werden; wobei die gepreßte pharmazeutische Dosierungsform eine Härte im Bereich von etwa 1,0 bis etwa 3,0 kp aufweist.

Revendications

1. Forme de dosage pharmaceutique à l'état comprimé, comprenant: au moins une particule enrobée comprenant au moins un produit pharmaceutique enrobé d'un enrobage donnant du goût;

un carbohydrate compressible, désintégrable à l'eau; et
un liant,

ladite forme de dosage ayant une dureté dans la gamme d'environ 1,0 à environ 3,0 kp et suffisante pour forcer ledit carbohydrate à se désintégrer dans les 30 secondes après administration orale pour ainsi permettre à ladite particule d'être avalée.

2. Forme de dosage pharmaceutique de la revendication 1, où le carbohydrate compressible est du mannitol, du sorbitol, du dextrose, du saccharose, du xylitol, du lactose ou un mélange de ceux-ci.

45. 3. Forme de dosage pharmaceutique de la revendication 1 ou 2, où ladite particule enrobée comprend au moins un produit pharmaceutique enrobé d'un mélange d'un premier polymère qui est un acétate de cellulose ou un acétate butyrate de cellulose et un second polymère qui est de la polyvinyl pyrrolidone ou de l'hydroxypropyl cellulose, où le rapport pondéral du premier polymère au second polymère est dans la gamme d'environ 90:10 à environ 50:50.

50. 4. Forme de dosage pharmaceutique selon l'une quelconque des revendications 1 à 3 qui est une pastille comprimée, comprenant:

des particules enrobées comprenant au moins un produit pharmaceutique enrobé d'un mélange d'un premier polymère qui est un acétate de cellulose ou un acétate butyrate de cellulose et d'un second polymère qui est de la polyvinyl pyrrolidone ou de l'hydroxypropyl cellulose, où le rapport pondéral du premier polymère au second polymère est dans la gamme d'environ 90:10 à environ 50:50; un carbohydrate désintégrable à l'eau, compressible, qui est du mannitol, sorbitol, dextrose, saccharose, xylitol, lactose, ou leurs mélanges; et

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un liant qui est de la cellulose, un dérivé cellulosique, de la polyvinyl pyrrolidone, de l'amidon, de l'amidon modifié ou un mélange de ceux-ci,

ladite pastille ayant une dureté dans la gamme d'environ 1,0 à environ 3,0 kp et ainsi ledit carbohydrate se désintègre après administration orale, permettant auxdites particules enrobées d'être avalées.

- 5 5. Pastille selon la revendication 4 ayant un diamètre d'environ 1,48 cm (7/16 pouce) à environ 1,91 cm (3/4 pouce), une épaisseur d'environ 0,13 cm (0,05 pouce) à environ 1,27 cm (0,5 pouce), et une dureté d'environ 1,5 à environ 2,5 kp.

- 10 6. Pastille de la revendication 4 ou de la revendication 5 comprenant:

environ 0,5 à environ 600 mg desdites particules enrobées;
environ 250 à environ 750 mg dudit carbohydrate; et
environ 20 à environ 100 mg dudit liant,

- 15 et qui comprend additionnellement, facultativement:

environ 4 à environ 10 mg d'un lubrifiant;
environ 1 à environ 10 mg d'une couleur;
20 environ 1 à environ 10 mg d'un édulcorant; et
environ 1 à environ 10 d'un arôme.

- 25 7. Forme de dosage pharmaceutique selon l'une quelconque des revendications 3 à 6 où la particule enrobée comprend environ 5 à environ 60 pour cent en poids du mélange des premier et second polymères.

- 30 8. Forme de dosage pharmaceutique selon l'une quelconque des revendications 1 à 7 où le produit pharmaceutique est acétaminophène, ibuprofène, flurbiprofène, naproxène, aspirine, pseudoéphédrine, phénylpropanolamine, maléate de chlorphéniramine, dextrométhorphan, diphenhydramine, famotidine, lopéramide, ranitidine, cimétidine, astémizole, terfénadine, carboxylate de terfénadine, certirizine, un sel pharmaceutiquement acceptable de ceux-ci ou un mélange, et où de préférence le produit pharmaceutique est acétaminophène, ibuprofène, lopéramide, famotidine ou aspirine.

- 35 9. Procédé de préparation d'une forme de dosage pharmaceutique à l'état comprimé, comprenant les étapes de:

- 40 35 former au moins une particule enrobée comprenant au moins un produit pharmaceutique enrobé d'un enrobage donnant du goût;
mélanger à sec ladite particule enrobée avec un carbohydrate compressible, désintégrable à l'eau et un liant et comprimer le mélange en une masse ayant une dureté suffisante pour forcer ledit carbohydrate à se désintégrer dans les 30 secondes après administration orale, pour ainsi permettre à ladite particule enrobée d'être avalée;
ou ladite forme de dosage pharmaceutique à l'état comprimé a une dureté dans la gamme d'environ 1,0 à environ 3,0 kp.

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